Inflammatory Crystallosis

IgA Gammopathy, Polyserositis and Extensive Fibrosis Associated With Intracellular Crystalline Protein Deposits

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WE PRESENT the case of a man with a plasma cell dyscrasia and widespread proteinaceous crystal deposition in phagocytic cells. These deposits were associated with extensive inflammation and fibrosis that gradually led to his death. This case is remarkable for the abundance of crystal deposition, and apparently unique because the distribution of the crystals appears to explain the clinical course of events.

Report of a Case

A 60-year-old man, a retired sheet-metal and insulation contractor, saw his physician in 1976 because of abdominal pain. After unrevealing clinical evaluation, a laparotomy was carried out and showed thickened peritoneum, adhesions and a chronic inflammatory mass at the hepatic flexure. Some crystals were seen within mononuclear cells in the specimen. After careful examination, no neoplasm, asbestos bodies or infectious agents were identified. He was taking no medications during this time.

Six months later the patient had lost 13.6 kg (30 lb) and the abdominal pain had returned. Evaluation then showed anemia and hypoalbuminemia. Skin testing showed anergy to six reagents, including purified protein derivative. Protein electrophoresis showed slight increases in α-1 and α-2 and moderate increase of β to 1.8 mg per dl. A fluorescent antinuclear antibody test was positive at 1/20, speckled. Coombs' tests were negative. Latex fixation was negative. A liver and spleen scan showed hepatomegaly. No abnormalities were found on abdominal and selective visceral arteriography. In December 1976 a second diagnostic laparotomy showed ascites and granulomatous mesenteric adenitis. Liver biopsy showed mild nonspecific triaditis. Bone marrow biopsy showed increased myeloid elements with normal maturation and increased plasma cells (3% to 4%). Ascitic fluid studies showed a sterile exudate. Subsequent cultures of fluid and lymph nodes were negative for fungi and tuberculosis.

In February 1977 the patient was readmitted for failure to gain weight and continued abdominal pain. He had lost 4.5 kg (10 lb) more and had new bilateral pleural effusions. Hepatomegaly, anemia and skin test anergy persisted. His pleural fluid had small numbers of mononuclear cells and a protein concentration of 3.6 mg per dl. Total serum protein was 6.0 and albumin was 2.8 mg per dl. Pleural biopsy gave inadequate tissue. Multiple radiologic studies were nondiagnostic and a third exploratory laparotomy was done. An intraoperative pancreatogram showed no abnormalities. Mesenteric and omental biopsy specimens showed dense serosal fibrosis. Because of severe dysphagia, a jejunostomy was carried out for feeding, and prednisone therapy was started at 30 mg per day given by mouth. Later in 1977 the prednisone dosage was tapered to 10 mg per day. That autumn, he had two episodes of partial small bowel obstruction, relieved after nasogastric suction and enemas.

From 1977 to 1980 the patient lived at home on a regimen of oral and jejunal feedings. In March 1980 he was readmitted with pericarditis and recurrent pleural effusions. The latter were drained, showing exudates with mostly mononuclear cells. Symptoms resolved with indomethacin therapy. Serum protein electrophoresis showed values for total protein of 7.6, albumin of 3.4, α-1 of 0.4, α-2 of 0.97, β of 2.09 and γ of 9.72 mg per dl. Immunoelectrophoresis showed a κ-reacting monoclonal IgA. Total IgA was 2,210 mg per dl. Pulmonary function tests showed a restrictive pattern with a vital capacity of 1.25 liters (30% predicted) and an FEV_1 (forced expiratory volume in one second) of 1.2 liters.

In May 1980 he had two episodes of aspiration. Aperistalsis of the esophagus was demonstrated, with aspiration of barium. Hepatomegaly and new jugular venous distension were noted. Nasogastric feedings led to more aspiration, so a gastrostomy was done. Prednisone administration was continued at 10 mg per day and no other medicines were instituted.

In June 1980 he was readmitted with cachexia. Respirations were 24 per minute and pulse was 90. Rales, jugular venous distension and a summation gallop were present. There was no adenopathy and his hepatomegaly was unchanged from prior admissions. Hematocrit was 39%, leukocyte count was 10,000 per μl with 95 polymorphonuclear leukocytes and 4 band cells; platelets appeared normal. Results of electrolyte, renal, hepatic function and coagulation tests were unremarkable. The CH_{50} was 675 units (normal 800 to 1,650), the C3 was 48 (normal 90 to 120) and the C4 was 22 mg per dl (normal 11 to 75). Urine immunoelectrophoresis showed a trace of κ-reacting Bence-Jones proteins. The result of a Raji cell assay for immune complexes was 54 μg AHG (aggregated human gonadotropin) Eq per ml of serum (normal, less than 12). An x-ray film of the chest showed a widened cardiac silhouette and 1.2 cm of pleural thickening

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bilaterally. All radiographs showed osteoporosis, but no focal lesions were seen.

Repeat bone marrow biopsy showed slight plasmacytosis (3% to 4%) without confluence of cells or nuclear atypia. Intracellular crystals were seen in most phagocytic cells. Review of all previous biopsy specimens showed similar crystals, which on special stains appeared to be widespread, proteinaceous and located chiefly within macrophages. The hypothesis of a lymphoproliferative disorder producing a crystalline paraprotein with inflammatory properties was formulated and chemotherapy was initiated.

The hospital course was complicated by recurrent aspiration of oral secretions, pneumonitis and gastrointestinal bleeding. Antibiotic and diuretic therapy was started along with parenteral nutrition and transfusions. Chronic respiratory insufficiency developed, refractory to aggressive diuresis and pulmonary toilet. Renewed intestinal bleeding and worsening respiratory failure developed during the first cycle of cyclophosphamide, vincristine and prednisone. In agreement with the patient's and family's wishes, resuscitation was not attempted after the patient suffered a respiratory arrest.

Findings at Autopsy

An exuberant overgrowth of fibrous tissue obliterated the pleural, pericardial and peritoneal cavities. The retroperitoneal, mediastinal and cervical soft tissues were involved extensively as well. Some areas of fibrosis were quite dense and cell poor, while other areas were vascular, edematous and infiltrated by lymphocytes, plasma cells, neutrophils, eosinophils and macrophages. Other major findings were pulmonary edema, focal interstitial pneumonitis, mild cardiac hypertrophy with focal fibrosis, hepatic centrilobular congestion with necrosis, acute pancreatitis, osteoporosis and cachexia. Bone marrow samples showed moderate plasmacytosis as seen on antemortem biopsy specimens, but nowhere was there a confluence of cells or nuclear dystrophy indicative of a neoplasm. Using appropriate stains, no asbestos bodies, tubercle bacilli or fungi could be found.

Crystalline deposits were seen in neutrophils and macrophages of all inflammatory tissues (Figure 1). Similar crystals were found in marrow, splenic and hepatic macrophages (Figure 2), in renal tubular lumens and glomerular endothelial cells and focally within the fibrous interstitium of the heart, lungs, kid-

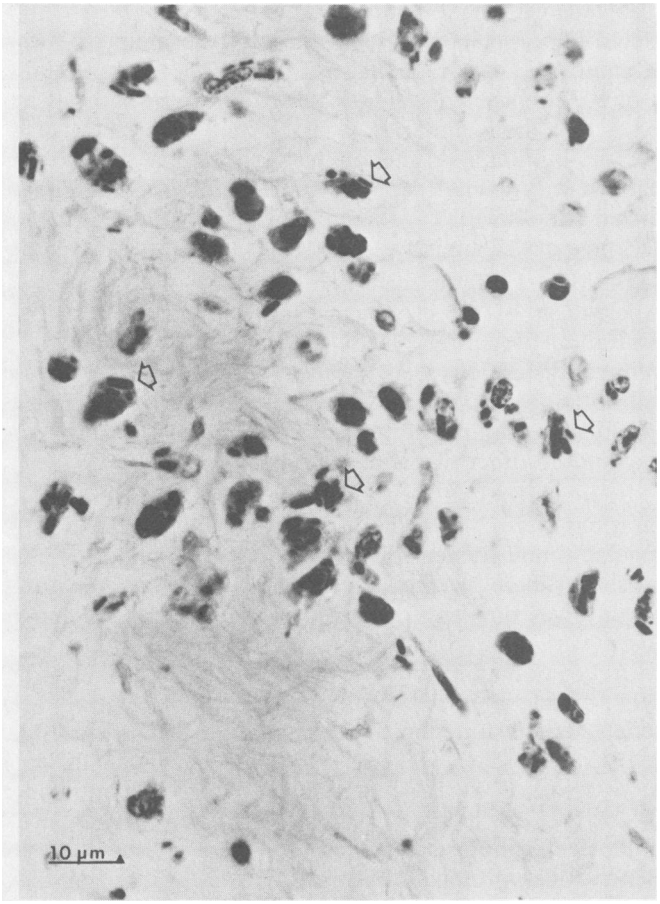

Figure 1.—Adhesions between pericardium and visceral pleura. Note cellular fibrous tissue with inflammatory cells. Arrows indicate densely stained intracellular crystals. (Modified Brown-Brenn stain, reduced from ×700.)

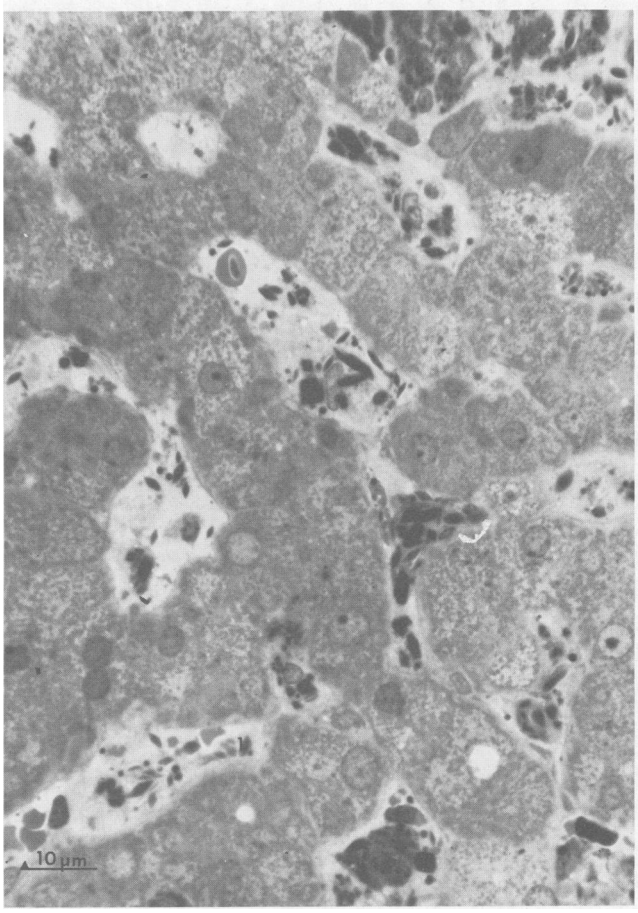

Figure 2.—Liver biopsy, epoxy section. Note crystals in Kupffer's cells. (Toluidine blue stain, reduced from ×700.)

neys, prostate and testes. The crystals also were abundant in the parenchymal cells of the posterior pituitary gland and the adrenal cortex.

Review of sections from all premortem biopsy specimens between 1976 and death showed the crystals in all samples of bone marrow, liver and mesenteric tissues. They appear to be an integral part of the necrotizing granulomas seen on the 1977 samples, being demonstrable readily within the cytoplasm of Langhans' cells.

The crystals were faintly eosinophilic, not acid-fast, and both Congo red and periodic acid-Schiff negative. They were azurophilic in smears with Romanovsky's stain and strongly fuchsinophilic. The Brown-Brenn stain (for bacteria in paraffin sections) gave a dramatic demonstration of the prevalence of the crystals (Figure 1). This staining pattern is typical for proteins.

The crystals remained unstained by immunochemical means, despite the use of antibodies to IgA, IgG, IgM, κ and λ light chains, J chains and secretory product. This was true despite use of fresh frozen or fixed paraffin sections, with or without prior partial trypsin digestion, and with indirect immunofluorescence or immunoperoxidase methods. In the bone marrow, plasmacytes showed a slight increase in the percentage of IgA positive cells, but a heterogeneous pattern of κ and λ reactivity.

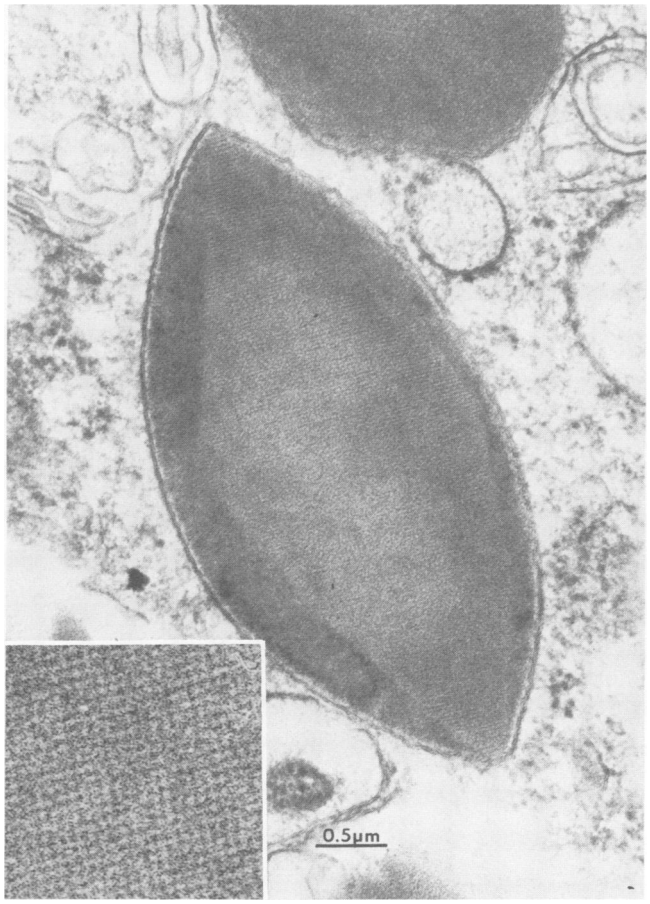

Figure 3.—Liver biopsy specimen with typical crystal in Kupffer's cell. Note surrounding unit membrane and lamellar internal structure of crystal. Electron micrography (×12,500). Insert: electron diffraction image (×33,000).

With electron microscopy, crystals were seen chiefly in macrophages and Kupffer's cells, less often in granulocytes and infrequently in plasma cells. Crystals were 0.9 to 15 μm in maximum dimension, often of rhomboid shape with sharp margins, and were bounded by a unit membrane like that of a lysosome. The interior of the crystals had a fine granular matrix, and in some a clearly discernible substructure of parallel lines could be seen (Figure 3). Structural analysis was carried out on an electron microscope fitted with a goniometer stage tilted until two crystal axes were apparent (insert, Figure 3). Fourier transformation of the digitized image was used to analyze its diffraction pattern, showing a cubic lattice structure with a unit cube side dimension of 55 nm. Further analysis of the crystals has not been possible so far.

Comments and Discussion

To summarize, the patient had progressive polyserositis of unknown cause, leading to widespread massive fibrosis with restrictive pleural and pericardial disease. Biopsy and autopsy studies showed widespread deposition of proteinaceous crystals in the reticuloendothelial system, marrow and all areas of fibrosis, including the serosal surfaces. Although an IgA-κ-reacting light chain was present in the serum, we were unable to find any immunochemical staining in the crystals or clear evidence of a monoclonal plasma cell proliferation.

Intracellular crystalline deposits have been reported in myeloma and in B-cell neoplasms. The latter are usually in cases of patients with typical chronic lymphocytic leukemia who have crystals described incidentally in a subpopulation of their blood lymphocytes.[1-8] Crystals have also been shown in the plasma cells of Waldenstrom's macroglobulinemia,[9] multiple myeloma,[9,10] gastric plasmacytoma[11] and other cases of less aggressive plasma cell dyscrasias.[12,13] Finally, Mullen and Chalvardjian[14] described a patient with bulky myeloma and hyperviscosity. He had widespread deposition of crystals with a rhomboid shape and staining characteristics very similar to the current case. Their crystals had no internal periodicity when viewed with an electron microscope, and did not react with immunochemical reagents. In all the above cases, the clinical course of the patients involved did not appear to correlate with the presence of tissue or intracellular crystals.

Polyserositis has been a feature of many different disease processes. Our patient's clinical course, physical findings and laboratory and pathologic data do not support diagnoses of lupus, other collagen vascular disorders, vasculitis, angioimmunoblastic lymphadenopathy or sarcoidosis. Infectious causes were considered and none were found, despite extensive and repeated biopsy and culture. Industrial exposures, particularly

to asbestos, could not be supported pathologically, nor could a diagnosis of retroperitoneal fibrosis.

The staining characteristics of the crystals and their appearance on electron microscopy suggest that they are protein aggregates with little or no polysaccharide. The lack of reaction with antibody reagents is puzzling, and there are several possible explanations. It is possible that the crystalline array may have shielded antigenic sites, preventing binding of our reagents. Since the presence of immune complexes was suggested by a Raji cell assay, the appropriate binding sites for our reagents may already be occupied in the complexes, which then crystallized and were engulfed by phagocytic cells. Another alternative is that the crystal protein may be an incomplete immunoglobulin or light chain without fully developed binding sites for our reagents. This might be due to defective glycosylation of the paraprotein, or alteration of its structure during secretion from the cells of origin.[15,16] Finally, the protein in the crystals may not be a component of immunoglobulin at all. However, we favor the hypothesis that the crystals are some form of immunoglobulin paraprotein.

The role of the crystals in the pathogenesis of the inflammatory response is obscure. They may be resistant to phagocytic digestion, leading to eventual cellular engorgement, rupture and release of inflammatory mediators. This would be analogous to the effect of gouty crystals or asbestos bodies on neutrophils. Alternatively, crystalline protein deposition may be a consequence of this patient's inflammatory response, rather than a cause. Unfortunately, our histochemical and electron microscopic studies do not further our insight into these possibilities.

In conclusion, we have described the combination of an IgA gammopathy, polyserositis and progressive massive fibrosis, associated with widespread deposition of intracellular protein crystal in all areas of inflammation. We suggest that this is a very unusual consequence of a plasma cell dyscrasia, an inflammatory crystallosis.

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Cardiac Presentation of a Bronchogenic Cyst

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BRONCHOGENIC CYSTS are congenital malformations usually identified in infants and children because of pulmonary infection or respiratory compromise.[1,2] In adults, clinical manifestations are infrequent and the cysts are part of the differential diagnosis of mediastinal tumors.[3] The patient in this report presented with cardiovascular findings, suggestive of mitral stenosis, caused by a bronchogenic cyst.

Report of a Case

An asymptomatic 24-year-old woman, a medical technician, was a control subject for a new electrocardiographic machine in her hospital and a question of an abnormality was raised. Subsequent review showed a normal tracing. She was unaware of a heart murmur since childhood. On examination, findings included an accentuated S_1, a grade 2/6 systolic murmur at the left sternal border and an early grade 2/4 diastolic rumble at the apex which was louder after exercise.

On an x-ray film of the chest, heart size was normal and the lung fields were clear but a mass posterior and superior to the left atrium elevated and compressed the left mainstem bronchus. A fine rim of calcium was present at the margins of the mass (Figure 1). M-mode and two-dimensional echocardiography showed a normal mitral valve. In the region of the left atrium, a mass with an echodense rim was identified but it was unclear whether it was intraatrial or extraatrial in location (Figure 2).

On cardiac catheterization, rest and exercise pressures and flows were within normal limits. Results of a left ventriculogram were normal. On the pulmonary venous phase of a pulmonary artery injection, the

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